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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,804	11/10/2005	Magali Williamson	BJS-620-373	4496
23117 7590 09/25/2009 NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203				
EXAMINER				
REDDIG, PETER J				
ART UNIT		PAPER NUMBER		
1642				
MAIL DATE		DELIVERY MODE		
09/25/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/536,804

**Applicant(s)**

WILLIAMSON ET AL.

**Examiner**

PETER J. REDDIG

**Art Unit**

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 76-106, 109 and 111-114 is/are pending in the application.
- 4a) Of the above claim(s) 76-105 and 112-114 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 106, 109, 111 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. The Amendment filed June 8, 2009 in response to the Office Action of March 6, 2009 is acknowledged and has been entered.
2. Claims 106, 109 and 111 have been amended. Claims 76-105 and 112-114 have been previously withdrawn
3. Claims 106, 109 and 111 are currently under consideration as drawn to the species mutation site 5653 of the plexinB1 coding sequence and the A5653G mutation.

### *Rejections Maintained*

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 106, 109 and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in section 4, pages 3-10 of the Office Action of March 6, 2009.

Examiner argued:

One cannot extrapolate the teachings of the specification to the enablement of the claims because one of skill in the art would not be predictably able use changes in either the wild type plexinB1 or the A5653G mutant to identify or obtain a putative anti-cancer agent. Although the A5653G mutation is found in primary and metastatic prostate tumors, this same mutant plexinB1 reduces the tumorigenicity of cells *in vivo*. Thus, it is not clear if this mutation is a positive or negative regulator of prostate tumor or any tumor formation as the mutation appears to be associated with both positive and negative regulation of tumor formation and one of skill in the art would not predictably know what change in expression of the A5653G mutant B1 nucleic acid would be important for affecting tumor formation and would not predictably be able to identify and/or obtain a compound as a putative anti-cancer agent based on change in expression of the A5653G mutant plexinB1. Thus, undue experimentation would be required for identifying and/or obtaining a putative anti-cancer agent by the claimed method.

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Additionally, it is not predictable that determining an increase in the wild-type plexinB1 would lead to the identification of a putative anti-cancer agent. Although the specification teaches that the expression of the wild-type plexin B1 suppresses tumor formation, Mack and Gish (US Pat. App. Pub. 2004/0005563, June 17, 2002) teach that plexin B1 is upregulated in ovarian cancer, see Table 14A and para. 0348 of the published application and Vogelstein et al. (US Pat. App. Pub 2005/0047996, October 9, 2001) teach that plexin B1 is upregulated in colorectal cancer, see Table 1. Thus, given that plexin B1 is upregulated in ovarian and colorectal cancers, the determination of an increase in the wild-type plexin B1 by a test compound would not predictably identify a putative anti-cancer agent. Thus, undue experimentation would be required for identifying and/or obtaining a putative anti-cancer agent by the claimed method.

Furthermore, given that A5653G mutant plexin B1 has only be identified in prostate cancers, one of skill in the art would not predictable expect that agents that affect the expression of this mutant plexinB1 nucleic acid would be putative anti-cancer agents for any cancer because it is well known in the art that cancers are heterogeneous in phenotype and genes expressed and cancer therapeutics are not predictably effective for all cancers.

In particular, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between the A5653G mutant plexin B1 and prostate cancer, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3<sup>rd</sup> col. Furthermore, Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. Chemotherapy of Cancer; Second edition; John Wiley & Sons : New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably extrapolate any potential correlation between an A5653G mutant plexin B1 directed anti-cancer agents and prostate cancer sensitivity to such an agent in any tumor type based on the information in the specification and known in the art without undue experimentation.

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Furthermore, one of skill in the art would not predictably expect that all of the broadly claimed mutants of plexinB1 to be associated with cancer and thus an effect on their expression would not predictably be useful for identifying a compound as a putative anti-cancer agent. It is noted that the specification teaches that a mutant plexinB1 nucleic acid may comprise a nucleotide sequence which has one or more mutations relative to the wild-type plexinB1 nucleotide sequence, as set out in AB007867. The mutations may be deletions, insertions or substitutions of one or more nucleotides see para. 0014 of the published application. Given the above and given that claims are drawn to contacting "a" plexin B1 nucleic acid, which reads on fragments, which comprises one or more mutations in a coding region of the nucleic acid, the broadest reasonable interpretation of the claims is that the claims are not limited to any specific plexinB1 mutants and the plexinB1 mutants can comprise nucleic acids that are completely distinct from plexinB1. Furthermore, given claims 108 and 109 are indefinite in lacking a point of reference, these claims are also not limited to a particular site of mutation within the coding region of the plexinB1 nucleic acid and the plexinB1 mutants can comprise nucleic acids that are completely distinct from plexinB1.

It would not be expected that such a diverse array of mutants of plexin B1 would predictably be associated with cancer given that even naturally occurring gene variants, such as splice variants, do predictably have the same expression pattern or encode proteins with the same function as the related variants.. In particular, Benedict et al (J. Exp. Medicine, 2001, 193(1) 89-99) specifically teach that two splice isoforms of terminal deoxynucleotide transferase (a long form and a short form) enter the nucleus but have different activity, the long form does not catalyze nontemplated nucleotide addition but rather modulates the activity of the short form (see abstract). Jiang et al (JBC, 2003, 278(7) 4763-4769) specifically teach that the type 3 Ca<sup>2+</sup> release channel, RyR3 exhibits strikingly different pharmacologic and functional properties depending on the tissues in which it resides. Upon examination, seven tissue specific alternatively spliced variants of RyR3 were detected. One of the variants was unable to form a functional channel but was able to suppress the activity of a different release channel. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). The abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1, which is present in brain and endocrine cells, latrophilin-2, which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teaches that the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer cells in contrast to standard CD44. These references serve to demonstrate that one of skill in the art cannot anticipate the biological activity of the proteins encoded by the broadly claimed plexinB1 mutants or the tissue distribution of the claimed mutants based on the biological activity of the protein encoded by the wild-type or tissue distribution of the wild-type nucleic acid or other mutants of plexinB1. Thus, even if it were found that the examination of the expression of the A5653G plexin B1 mutant could be used as claimed, undue experimentation would be required to use the broadly claimed mutants or even other mutations at position 5653 for the identification of putative anti-cancer agents.

The specification provides insufficient guidance with regard to the issues set forth

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above and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicants argue that the Section 112, first paragraph "enablement", rejection of claims 106, 109 and 111 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments and the attached Wong et al ("Plexin-B1 mutations in prostrate cancer" PNAS November 27, 2007, vol. 104, no. 48, 19040-19045).

Applicants argue that the Examiner is understood to believe that the specification lacks experimental data which shows that the claimed mutations are involved in the etiology of cancer, so one of skill in the art could, according to the Examiner, not predictably use the claimed methods for identification of an anticancer drug without undue experimentation.

Applicants argue that the Examiner is requested to see the attached Wong et al, which is a peer-reviewed publication co-authored by the present inventors which contains the mutation data which is set out in the instant specification. Wong et al also contains additional data which shows the functional effects of four separate plexinB1 mutations (A5359G; A5653G; T5714C and C5060T) in cultured cells.

Applicants argue that all four plexinB1 mutants were shown to decrease the shrinkage or collapse of COS-7 cells relative to wild-type plexinB1 (Wong et al; figure 3c) and to significantly increase the adhesion of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 3d).

Applicants argue that furthermore, plexinB1 mutation was also shown to significantly increase the rate of migration of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 4a) and to increase the invasive capacity of HEK293 cells relative to wild-type plexinB1 (Wong et al; figure 4b). Expression of plexinB1 mutants in HEK293 cells was also shown to significantly increase the percentage of cell spreading and average cell size relative to expression of wild-type plexinB1 (Wong et al; figures 5a and 5b).

Applicants argue that in addition, mutation of plexinB1 is also shown to inhibit RacGTP and R-Ras binding (Wong et al; figures 5c, 6a and 6b), which may contribute to the observed increase in cell adhesion and motility (Wong et al; page 19044 col. 1 2nd para)

Applicants argue that the functional data set out in Wong et al provides further confirmation that plexinB1 mutation is functionally important in the etiology of cancer, and in particular cancer progression. For example, Wong et al states at page 19044 col. 1;

Together these results suggest that Plexin-B1 has a role in prostate cancer progression.

Applicants argue that Wong et al further state the following at page 19044 col. 2;

Plexin-B1 is likely to be a key player in cancer invasion and metastasis and is a potential target for anticancer therapy.

Applicants argue that it is therefore evident that plexinB1 mutations are involved in the etiology of cancer. The claimed methods could therefore be predictably used by one of ordinary skill in the art for identifying a compound as a putative anti-cancer agent.

Applicants' arguments have been considered, but have not been found persuasive because the functional studies of Wong et al. of the plexin B1 are based on *in vitro* studies in cell lines,

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which do not predictably extrapolate to *in vivo* anti-cancer activity. In particular, the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12: 320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al. further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2).

Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in *de novo* tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-

population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties *in vivo*. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist *in vivo*. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Thus, given the above the *in vitro* cell culture data presented Wang et al. do not provide enabling support for the claimed method, in the absence of data that the 5653 mutations affect cancer growth *in vivo*, such as in animal model system. Furthermore, the teachings of Wang et al. are not commensurate in scope with the claimed method as the claimed method encompasses a much broader array of mutations than those examined by Wang et al. Thus, given the unpredictability in the art previously set forth and above, the rejection is maintained for the reasons previously set forth and above.

Applicants argue that the Examiner's criticism of the applicants previous reliance on Wong et al (2007) PNAS 104 19040-19045 because the *in vitro* results "do not predictably extrapolate to *in vivo* anti-cancer activity" (see page 7 of the Office Action dated March 6, 2009) is not understood as the present claims define "methods of identifying a compound as a putative anti-cancer agent" and not to specific compounds whose anticancer activity is predicted only from *in vitro* studies.

Applicants argue that one of ordinary skill in the art will appreciate that *in vitro* experiments are a useful tool to identify compounds as potential therapeutic agents. The fact that the *in vitro* experiments may not directly extrapolate to *in vivo* therapeutic activity does not demonstrate that the *in vitro* methods would require undue experimentation.

Applicants argue that *in vitro* assays are widely used throughout the pharmaceutical industry for early stage drug development (see figure 1 of Zips et al (in vivo 19:1-8 (2005)); of record) and are an important tool in identifying promising compounds for further study. Zip for example, states on page 3, left column, first paragraph:

Compared to animal tumor models, *in vitro* methods are less expensive and less time consuming, thereby allowing evaluation of large quantities of new anticancer agents. Molecular methods to prove and quantify the potential of several drugs to affect the molecular target...facilitate the selection of promising candidate drugs.

Applicants argue that *in vitro* assays are therefore used to identify compounds as possessing putative activity. These compounds are then extensively tested in subsequent stages of drug development, including in animal models, to assess whether they possess activity *in vivo*. Compounds which are found to be active *in vivo* may then be tested in the clinic.

Applicants argue that in other words, despite the fact that *in vitro* activity may not necessarily extrapolate to *in vivo* anti-cancer activity, *in vitro* assays are still an essential part of drug development in identifying initial hits which are worthy of further investigation and can be performed without requiring undue experimentation. The important role of *in vitro* methods in the early stages of drug discovery is confirmed on page 6, left column "Conclusion" of Zips et al, which states;

A step-wise procedure from *in vitro* to *in vivo* seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing.

Applicants argue that it is apparent, for example from Zips et al. that, despite their potential pitfalls and limitation, *in vitro* methods play an important role in drug testing (see page 3, left column). The fact that not all compounds identified in an *in vitro* assay will successfully

progress through clinical trials does not make the *in vitro* assay any less useful in identifying putative promising drugs for further testing, nor does it support a conclusion that undue experimentation would be required to practice such methods.

Applicants argue that for completeness, the applicants note that the specification includes clinical data which demonstrates that there is a very high frequency of mutations in plexinB1 in prostate and breast cancer cells from patients. Cancer genesis and progression is driven by genetic changes, and these plexinB1 mutations are one of the most frequent genetic changes yet found in any form of cancer.

Applicants argue that the *in vitro* experimental data, for example in Wong et al, confirms that the identified *in vivo* mutations alter the function of cells *in vitro*.

Applicants argue that the combination of *in vivo* and *in vitro* data provides clear clinical evidence that the claimed plexinB1 mutations play a role in the etiology of cancer *in vivo*. This evidence was accepted by the Proceedings of the National Academy of Sciences USA during the peer-review process (.see Wong et al).

Applicants argue that the totality of evidence of record therefore demonstrates that one of ordinary skill could practice the claimed invention without requiring undue experimentation.

Applicants' arguments have been considered, but have not been found persuasive. Although *in vitro* assays with end points known to be relevant to cancer can be used in drug screening assays the claims are defining a new method of screening and neither the specification nor the art of record has established that determining the expression of plexin B1 nucleic acids with mutations at position 5653 or any other of the claimed mutations will indicate a compound is a putative anti-cancer agent for breast or prostate cancer. Although some of the claimed

mutations are found in breast and prostate cancer *in vivo*, this does not show that the mutations are causative of cancer or that the changes in the expression of these nucleic acids will affect a cancer's growth or development. Additionally, given that Wong et al. only examined the effect of these mutations *in vitro*, given the unpredictability of extrapolating *in vitro* assays to *in vivo* anti-cancer activity previously set forth, one of skill in the art cannot predictably extrapolate the teachings of the specification and the art of record to enable the claims without undue experimentation. Furthermore, the teachings of Wong et al. are not commensurate in scope with the claimed method as the claimed method encompasses a much broader array of mutations than those examined by Wong et al. (any mutation at the sites in claim 106) in breast or prostate cancer. Thus, given the unpredictability in the art previously set forth and above, the rejection is maintained for the reasons previously set forth and above.

5. Claims 106, 109, and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth in the Office Action of March 6, 2009, section 5, page 10-11.

Examiner argued:

The limitation of a "the plexinB1 coding sequence of AB0007867.1" claimed in Claims 106, 109, and 111 has no clear support in the specification and the claims as originally filed. A review of the specification as revealed support for AB007867.1, see page 8, line 29. Thus subject matter claimed in Claims 106, 109, and 111 broadens the scope of the invention as originally disclosed in the specification.

Applicants argue the amendment will obviate this rejection.

Applicants' argument has been considered, but has not been found persuasive because claims are still drawn to "the plexinB 1 coding sequence of AB0007867.1" and the specification only refers to AB007867.1, e.g. see page 6-line 4. Additionally, a review of the specification and claims as originally filed does not reveal support for SEQ ID NO: 112. Thus subject matter claimed in Claims 106, 109, and 111 broadens the scope of the invention as originally disclosed in the specification.

Applicants argue the amendment will obviate this rejection.

Applicants' argument has been considered, but has not been found persuasive because, a review of the specification and claims as originally filed does not reveal support for SEQ ID NO: 112. Thus subject matter claimed in Claims 106, 109, and 111 encompasses new matter relative to that originally disclosed in the specification and claims as originally filed.

It is noted that AB007867.1 was named in the original specification at page 6-line 5 and the documents mentioned in the specification were incorporated by reference, see p. 46-lines 30-32 of the original specification.

The attempt to incorporate subject matter, SEQ ID NO: 112, into this application by reference to AB007867.1 is ineffective because "essential material", i.e. material that provides written description, may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. See 37 CFR 1.57(c).

Additionally, a copy of the material incorporated by reference accompanied by a statement that the copy supplied consists of the same material incorporated by reference in the referencing application is required. See 37 CFR 1.57(e).

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance

with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Applicants may comply with 37 CFR 1.57(c) by inserting material by amendment that was previously incorporated by reference accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

### *Specification*

6. In the Office Action of March 6, 2009, section 7, page 12 Examiner argued:

The amendment filed December 24, 2008 was objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO: 111 and SEQ ID NO: 112.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicants' argue that the Appendix 1 to the Office Action dated March 6, 2009, provided by the Examiner demonstrates that the sequences referred to in the objected-to amendments to the specification are the same as the sequence referred to in the originally-filed specification. The Appendix 1 provided by the Examiner demonstrates that the SEQ ID NO: 112 referred to in the objected-to amendments to the specification was well known to those of ordinary skill in the art. The applicant's disclosure therefore the objected-to sequences in the originally-filed specification and withdrawal of the new matter objection is requested

Applicants' arguments have been considered, but have not been found persuasive because mere recitation of an accession number does not provide adequate support for the addition of SEQ ID NO: 111 and SEQ ID NO: 112 to the specification.

It is noted that AB007867.1 was named in the original specification at page 6-line 5 and the documents mentioned in the specification were incorporated by reference, see p. 46-lines 30-32 of the original specification.

The attempt to incorporate subject matter, SEQ ID NO: 112, into this application by reference to AB007867.1 is ineffective because “essential material”, i.e. material that provides written description, may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. See 37 CFR 1.57(c).

Additionally, a copy of the material incorporated by reference accompanied by a statement that the copy supplied consists of the same material incorporated by reference in the referencing application is required. See 37 CFR 1.57(e).

The incorporation by reference of SEQ ID NO: 112/AB007867.1 will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Applicants may comply with 37 CFR 1.57(c) by inserting material by amendment that was previously incorporated by reference accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter, SEQ ID NO: 111, into this application by reference to AB007867.1 is ineffective because AB007867.1 is not a protein sequence and because "essential material", i.e. material that provides written description, may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. See 37 CFR 1.57(c).

7. All other objections and rejections recited in Office Action of March 6, 2009 are withdrawn.
8. No claims allowed.
9. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R., 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R., 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/  
Examiner, Art Unit 1642